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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12N 15/57, 9/64, C07K 16/40, A61K 38/395, G01N 33/574</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/20140</b> <b>(43) International Publication Date:</b> 14 May 1998 (14.05.98)
<b>(21) International Application Number:</b> PCT/US97/19930 <b>(22) International Filing Date:</b> 5 November 1997 (05.11.97) <b>(30) Priority Data:</b> 60/030,761 6 November 1996 (06.11.96) US <b>(71) Applicant (for all designated States except US):</b> THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 22nd floor, 300 Lakeside Drive, Oakland, CA 94612-3550 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GRANGER, Gale, A. [US/US]; 31562 Santa Rosa, Laguna Beach, CA 92651 (US). GATANAGA, Tetsuya [JP/US]; Apartment A, 2008 Los Trancos Drive, Irvine, CA 92612 (US). <b>(74) Agents:</b> LEHNHARDT, Susan, K. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).			<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> ISOLATED TUMOR NECROSIS FACTOR RECEPTOR RELEASING ENZYME, COMPOSITIONS COMPRISING THE ENZYME AND METHODS OF THE USE THEREOF			
<b>(57) Abstract</b> <p>The present invention relates to methods of regulating TNF activity indirectly by regulating the activity or concentration of TNF receptor releasing enzyme (TRRE). Preferably, the TRRE activity is regulated local to the site of the condition to be treated. In the case of diseases associated with elevated levels of TNF, such as rheumatoid arthritis, TRRE is administered to the site of inflammation in an amount sufficient to decrease the local levels of TNF. In the case of diseases, such as cancer, that benefit from increased levels of TNF, the level of TRRE is decreased at the disease site.</p>			

# INTERNATIONAL SEARCH REPORT

national Application No  
PCT/US 97/19930

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C12N15/57 C12N9/64 C07K16/40 A61K38/395 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C12N C07K G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KATSURA K. ETAL.: "Identification of the proteolytic enzyme which cleaves human p75 TNF receptor in vitro." BIOCHEM. BIOPHYS. RES. COM., vol. 222, 15 May 1996, page 298-302 XP002058218 see the whole document	1-17,24, 37-43,50
Y		18,19, 44,45 20-23, 25-36, 46-49, 51-62
A	---	-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 March 1998

Date of mailing of the international search report

27. 03. 98

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/19930

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,0	KATSURA K. : "Identification and characterization of soluble TNF receptor releasing enzyme (TRRE) from PMA-stimulated human monocytic THP-1 cells" PROCEEDINGS AMERICAN. ASSN. CANCER RES. MEETING, vol. 37, 20 - 24 April 1996, page 492 XP002058219 see abstract	1-15,24, 37-41,50
X	--- EP 0 657 536 A (YEDA RES & DEV) 14 June 1995 cited in the application see abstract	24,50
A		1-23, 25-49, 51-62
Y	--- F.M. AUSUBEL ET AL., EDS.: "Current Protocols in Molecular Biology" 1987 , JOHN WILEY & SONS XP002058220 see page 10.0.1 - page 10.0.19 see figures 2,3	18,19, 44,45
A	-----	1-18, 37-45

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 97/19930

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/19930

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 20-23,29-36,46-49,55-62 are directed methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International Application No  
**PCT/US 97/19930**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0657536 A	14-06-95	AU 679559 B	03-07-97
		AU 7574294 A	04-05-95
		CA 2133872 A	13-04-95
		JP 7194376 A	01-08-95
		US 5665859 A	09-09-97
		ZA 9407962 A	21-11-95
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